CYCLOSERINE- cycloserine capsule
Purdue GMP Center LLC dba The Chao Center

DESCRIPTION SECTION

Cycloserine, 3-isoxazolidinone, 4-amino –, (R)– is a broad–spectrum antibiotic that is produced by a strain of Streptomyces orchidaceus and has also been synthesized. Cycloserine is a white to off–white powder that is soluble in water and stable in alkaline solution. It is rapidly destroyed at a neutral or acid pH.

Cycloserine has a pH between 5.5 and 6.5 in a solution containing 100 mg/mL. The molecular weight of cycloserine is 102.09, and it has an empirical formula of C3H6N2O2.

INACTIVE INGREDIENT SECTION

Each capsule contains cycloserine, 250 mg (2.45 mmol); D and C Yellow No. 10, FD and C Blue No. 1, FD and C Red No. 3, FD and C Yellow No. 6, gelatin, iron oxide, talc, titanium dioxide, and other inactive ingredients.

CLINICAL PHARMACOLOGY SECTION

After oral administration, cycloserine is readily absorbed from the gastrointestinal tract, with peak blood levels occurring in 4 to 8 hours.
Blood levels of 25 to 30 µg/mL can generally be maintained with the usual dosage of 250 mg twice a day, although the relationship of plasma levels to dosage is not always consistent. Concentrations in the cerebrospinal fluid, pleural fluid, fetal blood, and mother's milk approach those found in the serum. Detectable amounts are found in ascitic fluid, bile, sputum, amniotic fluid, and lung and lymph tissues. Approximately 65 percent of a single dose of cycloserine can be recovered in the urine within 72 hours after oral administration. The remaining 35 percent is apparently metabolized to unknown substances. The maximum excretion rate occurs 2 to 6 hours after administration, with 50 percent of the drug eliminated in 12 hours.

MICROBIOLOGY SECTION

Cycloserine inhibits cell–wall synthesis in susceptible strains of gram–positive and gram–negative bacteria and in Mycobacterium tuberculosis.

Susceptibility Tests

Cycloserine clinical laboratory standard powder is available for both direct and indirect methods1 of determining the susceptibility
of strains of mycobacteria. Cycloserine MICs for susceptible strains are 25 µg/mL or lower.

INDICATIONS & USAGE SECTION

Cycloserine is indicated in the treatment of active pulmonary and extrapulmonary tuberculosis (including renal disease) when the causative
organisms are susceptible to this drug and when treatment with the primary medications (streptomycin,

isoniazid, rifampin, and ethambutol) has proved inadequate. Like all antituberculosis drugs, cycloserine should be administered in conjunction with other effective chemotherapy and not as the sole therapeutic agent.
Cycloserine may be effective in the treatment of acute urinary tract infections caused by susceptible strains of gram–positive and gram–negative bacteria, especially Enterobacter spp. and Escherichia coli. It is generally no more and is usually less effective than other antimicrobial agents in the treatment of urinary tract infections caused by bacteria other than mycobacteria. Use of cycloserine in these infections should be considered only when more conventional therapy has failed and when the organism has been demonstrated to be susceptible to the drug.

CONTRAINDICATIONS SECTION

Administration is contraindicated in patients with any of the following:

Hypersensitivity to cycloserine

Epilepsy

Depression, severe anxiety, or psychosis

Severe renal insufficiency

Excessive concurrent use of alcohol

WARNINGS SECTION

Administration of cycloserine should be discontinued or the dosage reduced if the patient develops allergic dermatitis or symptoms of CNS toxicity, such as convulsions, psychosis, somnolence, depression, confusion, hyperreflexia, headache, tremor, vertigo, paresis, or dysarthria.

The toxicity of cycloserine is closely related to excessive blood levels (above 30 µg/mL), as determined by high dosage or inadequate renal clearance. The ratio of toxic dose to effective dose in tuberculosis is small.

The risk of convulsions is increased in chronic alcoholics.

Patients should be monitored by hematologic, renal excretion, blood level, and liver function studies.

PRECAUTIONS SECTION

Before treatment with cycloserine is initiated, cultures should be taken and the organism's susceptibility to the drug should be established. In
tuberculous infections, the organism's susceptibility to the other antituberculosis agents in the regimen should also be demonstrated.

Anticonvulsant drugs or sedatives may be effective in controlling symptoms of CNS toxicity, such as convulsions, anxiety, and tremor. Patients receiving more than 500 mg of cycloserine daily should be closely observed for such symptoms. The value of pyridoxine in preventing CNS toxicity from cycloserine has not been proved.

Administration of cycloserine and other antituberculosis drugs has been associated in a few instances with vitamin B12 and/or

folic–acid deficiency, megaloblastic anemia, and sideroblastic anemia. If evidence of anemia develops during treatment, appropriate studies and therapy should be instituted.

LABORATORY TESTS SECTION

Blood levels should be determined at least weekly for patients with reduced renal function, for individuals receiving a daily dosage of more
than 500 mg, and for those showing signs and symptoms suggestive of toxicity. The dosage should be adjusted to keep the blood level below 30 µg/mL.

DRUG INTERACTIONS SECTION

Concurrent administration of ethionamide has been reported to potentiate neurotoxic side effects.

Alcohol and cycloserine are incompatible, especially during a regimen calling for large doses of the latter. Alcohol increases the possibility and risk of epileptic episodes.

Concurrent administration of isoniazid may result in increased incidence of CNS effects, such as dizziness or drowsiness. Dosage adjustments may be necessary and patients should be monitored closely for signs of CNS toxicity.
Carcinogenesis, Mutagenicity, and Impairment of Fertility

Studies have not been performed to determine potential for carcinogenicity. The Ames test and unscheduled DNA repair test were negative. A study in 2 generations of rats showed no impairment of fertility relative to controls for the first mating but somewhat lower fertility in the second mating.

PREGNANCY SECTION

Pregnancy Category C

A study in 2 generations of rats given doses up to 100 mg/kg/day demonstrated no teratogenic effect in offspring. It is not known whether cycloserine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Cycloserine should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS SECTION

Because of the potential for serious adverse reactions in nursing infants from cycloserine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE SECTION

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS SECTION

Most adverse reactions occurring during therapy with cycloserine involve the nervous system or are manifestations of drug hypersensitivity. The following side effects have been observed in patients receiving cycloserine:

Nervous system symptoms (which appear to be related to higher dosages of the drug, i.e., more than 500 mg daily)

Convulsions
Drowsiness and somnolence
Headache
Tremor
Dysarthria
Vertigo
Confusion and disorientation with loss of memory
Psychoses, possibly with suicidal tendencies
Character changes
Hyperirritability
Aggression
Paresis
Hyperreflexia
Paresthesia
Major and minor (localized) clonic seizures
Coma

Cardiovascular

Sudden development of congestive heart failure in patients receiving 1 to 1.5 g of cycloserine daily has been reported

Allergy (apparently not related to dosage)

Skin rash

Miscellaneous

Elevated serum transaminase, especially in patients with preexisting liver disease

OVERDOSAGE SECTION

Acute toxicity from cycloserine can occur if more than 1 g is ingested by an adult. Chronic toxicity from cycloserine is dose related and can occur if more than 500 mg is administered daily. Patients with renal impairment will accumulate cycloserine and may develop toxicity if the dosing regimen is not modified. Patients with severe renal impairment should not receive the drug. The central nervous system is the most common organ system involved with toxicity. Toxic effects may include headache, vertigo, confusion, drowsiness,
hyperirritability, paresthesias, dysarthria, and psychosis. Following larger ingestions, paresis, convulsions, and coma often occur. Ethyl alcohol may increase the risk of seizures in patients receiving cycloserine.

The oral median lethal dose in mice is 5290 mg/kg.
Treatment

To obtain up–to–date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage,
consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Overdoses of cycloserine have been reported rarely. The following is provided to serve as a guide should such an overdose be ecountered.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

In adults, many of the neurotoxic effects of cycloserine can be both treated and prevented with the administration of 200 to 300 mg of pyridoxine daily.

The use of hemodialysis has been shown to remove cycloserine from the bloodstream. This procedure should be reserved for patients with
life-threatening toxicity that is unresponsive to less invasive therapy

DOSAGE & ADMINISTRATION SECTION

Cycloserine is effective orally and is currently administered only by this route. The usual dosage is 500 mg to 1 g daily in divided doses monitored by blood levels.2 The initial adult dosage most frequently given is 250 mg twice daily at 12–hour intervals for the first 2 weeks. A daily dosage of 1 g should not be exceeded.

HOW SUPPLIED SECTION

Cycloserine is available as a 250 mg capsule with an opaque red cap and opaque gray body imprinted with "CHAO" and "F04" in edible black ink on both the cap and the body.

Bottles of 40 NDC 13845-1201-3

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

REFERENCES SECTION

1. Kubica GP, Dye WE: Laboratory methods for clinical and public health - mycobacteriology, US Department of Health, Education, and Welfare, Public Health Services, 1967, pp47-55, 66-70.

2. Jones LR: Colorimetric determination of cycloserine, a new antibiotic. Anal Chem 1956; 28:39.

The Chao Center for Industrial Pharmacy and Contact Manufacturing West Lafayette, IN, 47906, USA

Literature revised 14 JANUARY 2009

LM000265.00 PRINTED IN USA

PACKAGE LABEL PRINCIPAL DISPLAY PANEL

CYCLOSERINE Capsules, USP 250mg THE CHAO CENTER NDC 13845-1201-3 40 capsules Rx only

Usual Initial Adult Dose: One capsule (250 mg) twice a day at 12 hour intervals. See accompanying literature. Dispense in a tight container.

WARNING: Potent drug. May cause serious reactions in some individuals. Use in patients under close medical supervision. Read accompanying literature before using.

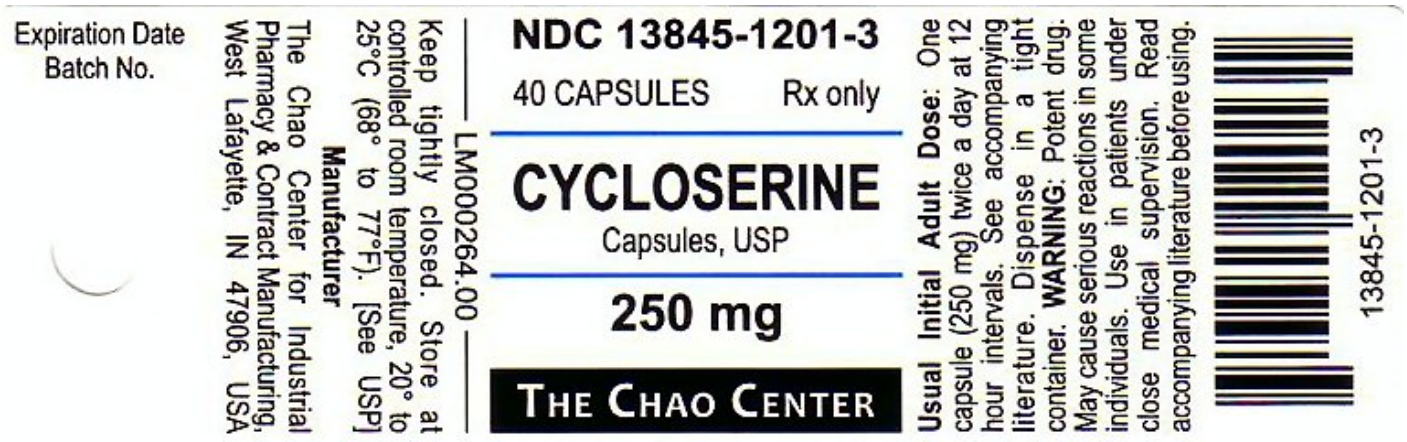
13845-1201-3

LM000264.00

Keep tightly closed. Store at controlled room temperature, 20 degrees to 25 degrees C (68 degrees to 77 degrees F). [see USP]

Maunfacture The Chao center for Industrial Pharmacy and Contract Manufacturing, West Lafayette, IN 47906, USA

Expiration Date Batch No.



CYCLOSERINE

cycloserine capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13845-1201
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CYCLOSERINE (UNII: 95IK5KI84Z) (CYCLOSERINE - UNII:95IK5KI84Z)	CYCLOSERINE	250 mg in 250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
GELATIN (UNII: 2G86QN327L)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	
SODIUM PROPIONATE (UNII: DK6Y9P42IN)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
BUTYLPARABEN (UNII: 3QPI1U3FV8)	
METHYLPARABEN (UNII: A2I8C7HI9T)	

Product Characteristics

Color	red (Opaque Red 353) , gray (Opaque Grey 284)	**Score**	no score
Shape	CAPSULE (CHAOFO4)	**Size**	10mm
Flavor		**Imprint Code**	CHAOFO4
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13845-1201-3	40 in 1 BOTTLE	03/01/2009	
1	NDC:13845-1201-1	250 mg in 1 CAPSULE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA060593	03/01/2009	

Labeler - Purdue GMP Center LLC dba The Chao Center (159802532)

Registrant - Purdue GMP Center LLC dba The Chao Center (159802532)

Establishment

Name	Address	ID/FEI	Business Operations
Purdue GMP Center LLC dba The Chao Center		159802532	manufacture(13845-1201)

Revised: 12/2018 Purdue GMP Center LLC dba The Chao Center